Another version of the amended claims, showing the changes relative to the previous version, is appended. Additions are shown by underlining. Deletions are shown by strikethrough rather than bracketing since the claims may contain bracketing that is to remain. No new matter has been added.

Claims 2, 6, 10, 15-21 and 28-29 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite, the examiner asserting that step (c) in claims 28-29 is vague. Responsive thereto applicants have amended their claims in order to more particularly point out and distinctly claim their invention. Thus, step (c) in claims 28-29 now recites:

(c) 0.1 to 80 % by weight of a lipophilic component which comprises a natural or synthetic or a partially synthetic C_4-C_{18}triglyceride, and a lipophilic pharmaceutical active agent, in which aqueous nanodispersion any pharmaceutically active agent is lipophilic and is always present in component (c).

Applicants aver this is neither vague not indefinite.

In claims 6 and 10 applicants replace "which is characterised in that" by the standard transitional phrase "wherein" as the examiner suggests. Also, in claim 10 "selected from the group consisting of" has been inserted " as the examiner suggests.

Applicants respectfully point out that claim 15 does not recite "the pharmaceutical end formulation". The word "end" was deleted in applicants' first amendment, mailed on April 16, 2000. See page 2, 6 lines from the end thereof. The examiner is requested to correct any PTO error in this regard.

Claims 16-19 are composition claims. But they depend on process claim 28. Accordingly they have been amended to depend on composition claim 29.

It is respectfully submitted that all the claims submitted for reconsideration are in good formal order. Reconsideration and withdrawal of the rejection of claims 2, 6, 10, 15-21 and 28-29 under 35 U.S.C. §112, second paragraph is therefore solicited.

Claims 2, 6, 10, 15-21 and 28-29 are now rejected under 35 U.S.C. § 102(b) as being anticipated by Weder et al., WO 96/37192. The examiner asserts that the instant claims are directed to aqueous nanodispersion formulations consisting essentially of

(a) 0.1 to 30 % by weight of a phospholipid,

(b) 1 to 50 % by weight of polyoxyethylene coemulsifiers,

(c) 0.1 to 80 % by weight of a lipophilic component which is a natural or synthetic or a partially

synthetic C_4-C_{18}triglyceride, and a lipophilic active agent, and

(d) 0.63 to 14.2 % by weight of ethanol, and

(e) a water phase, and to methods of preparing said nanodispersion formulations. Applicants note that the sum of (a), (b), (c) and (d) is 100 % by weight in independent claims 28 and 29. Hence all the remaining claims incorporate this limit.

In contrast thereto, WO 96/37192 discloses a pharmaceutical or cosmetic composition comprising

(a) a sphingolipid,

(b) a phospholipid,

(c) a fatty acid ester of polyoxyethylene sorbitan,

(d) a C_2-C_4alkanol,

(e) a therapeutic agent,

(f) a triglyceride and

(g) water-soluble or lipid-soluble additives.

Applicants aver that present independent claims 28 and 29 exclude the reference component (a), i.e. the essential sphingolipid component of the '192 reference, by using "consisting essentially of" rather than "comprising" language and by the proviso that the sum of claimed components (a), (b), (c) and (d) is 100 % by weight.

Weder et al., WO 96/37192 fails to disclose any aqueous nanodispersion formulation consisting essentially of claimed components (a), (b), (c) and (d) wherein the sum of claimed components (a), (b), (c) and (d) is 100 % by weight. Therefore, present claims 2, 6, 10, 15-21, 24 and 28-29 are clearly distinguished from the disclosure of this reference.

Reconsideration and withdrawal of the rejection of claims 2, 6, 10, 15-21 and 28-29 under 35 U.S.C. § 102(b) as being anticipated by Weder et al., WO 96/37192 is respectfully solicited in light of the remarks *supra*.

Claims 2, 6, 10, 15-21 and 28-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Weder et al., U.S. Patent 5,997,888 in view of WO 96/37192.

The examiner asserts that Weder et al. discloses cosmetic compositions containing nanodispersions comprising a fatty acid ester of a polyoxyethylene sorbitan, a phospholipid, 0.65% of ethanol, a water

phase, and a lipophilic active agent such as tocopherol acetate or vitamin A palmitate, and conventional mixing methods (e.g. utilizing magnetic stirring bars - see col. 8, lines 2-5).

The examiner admits that Weder et al. does not use a combination of a triglyceride and the lipophilic active agent. But the examiner relies on WO 96/37192 to show that the use of a triglyceride to improve stability and solubility of a lipophilic drug in an aqueous emulsion system is conventional. The examiner asserts that the claimed pharmaceutical compositions and process to make them are therefore rendered obvious by the teachings of Weder et al. in view of WO 96/37192.

Applicants respectfully traverse this rejection for the reasons which follow.

WO 96/37192 discloses a sphingolipid-containing pharmaceutical or cosmetic composition which further comprises

(a) a phospholipid,
(b) a fatty acid ester of polyoxyethylene sorbitan,
(c) a C_2-C_4alkanol,
(d) a therapeutic agent,
(e) a triglyceride and,
(f) water-soluble or lipid-soluble additives.

This reference teaches the therapeutic or cosmetic use of the important group of sphingolipids and enables the preparation of suitable topical or parenteral dosage forms containing this active ingredient. This is achieved with a combination of phospholipids and a partial fatty acid ester of polyoxyethylene sorbitan which provides a finely dispersed sphingolipid-containing system.

The assertion that the use of a triglyceride improves the stability and solubility of lipophilic drugs in an aqueous emulsion system is the teaching of this reference is seen to be hindsight speculation. Rather, it is the clear teaching that the combination of phospholipids and a partial fatty ester of polyoxyethylene sorbitan enables the cosmetic or pharmaceutical use of sphingolipids. The reference is silent on the function of the triglyceride.

Weder et al., U.S. Patent 5,997,888, was previously discussed in applicants' last amendment. The examiner admits that the Weder et al. '888 patent does not use a combination of a triglyceride and the lipophilic active agent.

Applicants regard the '888 patent as the most relevant prior art. Accordingly, in applicants' last amendment they submitted a declaration of Dr. Andreas Supersaxo, an expert in the area of drug delivery systems, who is the first-named inventor of the present application. Dr. Supersaxo compared the nanodispersions of the present invention to those of the Weder et al. '888 patent and explained why Weder's polydisperse formulations would not be useful for pharmaceutical and cosmetic applications.

There is no evidence in the record that this declaration was considered.

In *Stratoflex, Inc. v. Aeroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983), the Court stated that

> evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.

Regardless of whether the prima facie case would have been characterized as strong or weak, the examiner must consider all of the evidence anew. The process is as stated in *In re Rinehart*, 189 USPQ 143, 147 (C.C.P.A. 1976):

> When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability.

Totally ignoring the submitted objective evidence of unobviousness is clearly erroneous. Applicant avers that the objective evidence overcomes the present ground of rejection for the reasons previously advanced. Reconsideration and withdrawal of the rejection of claims 2, 6, 10, 15-21 and 28-29 under 35 U.S.C. § 103(a) as being unpatentable over Weder et al., U.S. Patent 5,997,888 in view of WO 96/37192, is therefore respectfully solicited.

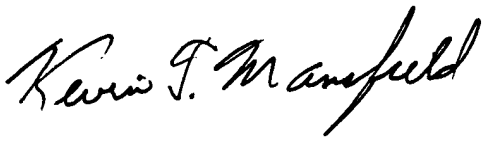
Claims 2, 6, 10, 15-21 and 28-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-45 of copending application number 09/306,005. As the examiner points out at the top of page 7, a non-statutory double patenting rejection can be overcome with a terminal disclaimer.

Responsive thereto, a terminal disclaimer with respect to copending application number 09/306,005 accompanies this Amendment.

Since there are no other grounds of objection or rejection, passage of this application to issue with claims 2, 6, 10, 15-21, 24 and 28-29 is earnestly solicited.

Applicants submit that the present application is in condition for allowance. In the event that minor amendments will further prosecution, Applicants request that the examiner contact the undersigned representative.

Respectfully submitted,



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APPENDIX: Marked up version of amended claims.

2. (twice amended) A method ~~Method~~ according to claim 28, wherein ~~which is characterised in that~~ step (α) is carried out in an anhydrous medium.

6. (thrice amended) A method ~~Method~~ according to claim 28, wherein ~~which is characterised in that~~ the nanodispersion comprises as component

(a) a phospholipid, a hydrated or partially hydrated phospholipid, a lysophospholipid, or mixtures thereof.

10. (thrice amended) A method ~~Method~~ according to claim 28, wherein ~~which is characterised in that~~ the nanodispersion comprises ~~as~~ at least one component (b) selected from the group consisting of polyethoxylated sorbitan fatty acid esters, polyethoxylated fatty alcohols, polyethoxylated fatty acids, polyethoxylated vitamin E derivatives, polyethoxylated lanolin and derivatives thereof, polyethoxylated fatty acid partial glycerides, polyethoxylated alkylphenols, polyethoxylated fatty alcohols and salts thereof, polyethoxylated fatty amines and fatty acid amides and polyethoxylated carbohydrates.

16. (twice amended) A pharmaceutical liquid formulation in the form of an injectable solution, infusion solution, drops, spray, aerosol, emulsion, lotion, suspension, drinking solution, gargle or inhalant, which comprises a nanodispersion as defined in claim ~~28~~29.

17. (twice amended) A pharmaceutical semisolid formulation in the form of an ointment, oil-in-water emulsion, water-in-oil emulsion, gel, lotion, foam, paste, suspension, ovula or plaster, which comprises a nanodispersion as defined in claim ~~28~~29.

18. (twice amended) A pharmaceutical solid formulation in the form of a tablet, coated tablet, capsule, granules, effervescent granules, effervescent tablet, lozenge, sucking and chewing tablet, suppositories, implant, lyophilisate, adsorbate or powder, which comprises a nanodispersion as defined in claim ~~28~~29.

19. (twice amended) A matrix- or membrane-controlled pharmaceutical application system in the form of an oros capsule, transdermal system or injectable microcapsule, which comprises a nanodispersion as defined in claim ~~28~~29.

28. (thrice amended) A method of preparing a pharmaceutical formulation of a lipophilic pharmaceutical active agent in the form of an aqueous nanodispersion, which steps consist essentially of

(α) mixing the components

(a) 0.1 to 30 % by weight of a phospholipid,

(b) 1 to 50 % by weight of a polyoxyethylene coemulsifier,

(c) 0.1 to 80 % by weight of a lipophilic component which comprises ~~is~~ a natural or synthetic or a partially synthetic C_4-C_{18}triglyceride, and a lipophilic pharmaceutical active agent, in which aqueous nanodispersion any pharmaceutically active agent is lipophilic and is always present ~~as~~ in component (c), and

(d) 0.63 to 14.2 % by weight of ethanol, with the proviso that the sum of (a), (b), (c) and (d) is 100 % by weight,

in conventional stirring apparatus until a homogeneous clear liquid is obtained and

(β) adding the liquid obtained in step (α) to a water phase, wherein (β) is carried out in the absence of high shear or cavitation forces, and wherein the particles in the nanodispersion have an average diameter <50 nm.

29. (thrice amended) An aqueous nanodispersion of a lipophilic pharmaceutical active agent, which consists essentially of

(a) 0.1 to 30 % by weight of a phospholipid,

(b) 1 to 50 % by weight of a polyoxyethylene coemulsifier,

(c) 0.1 to 80 % by weight of a lipophilic component which comprises ~~is~~ a natural or synthetic or a partially synthetic C_4-C_{18}triglyceride, and a lipophilic pharmaceutical active agent, in which aqueous nanodispersion any pharmaceutically active agent is lipophilic and is always present ~~as~~ in component (c), and

(d) 0.63 to 14.2 % by weight of ethanol, with the proviso that the sum of (a), (b), (c) and (d) is 100 % by weight, plus

(e) a water phase,

which formulation is obtainable by

(α) mixing the components (a), (b), (c), and (d) until a homogeneous clear liquid is obtained, and

(β) adding the liquid obtained in step (α) to the water phase, wherein step (β) is carried out in the absence of high shear or cavitation forces, and whereby the particles in the nanodispersion have an average diameter <50 nm.